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Advances in Process Control

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1. Introduction

Computer control of industrial processes began in 1959, when a computer was first used to control a polymerization unit in a Texaco refinery. There has been a dynamic development fueled by drastic advances in process understanding, control theory, sensors and computer technology. The following quote from a study by the US National Research Council [1] indicates the economic importance of computer based control:
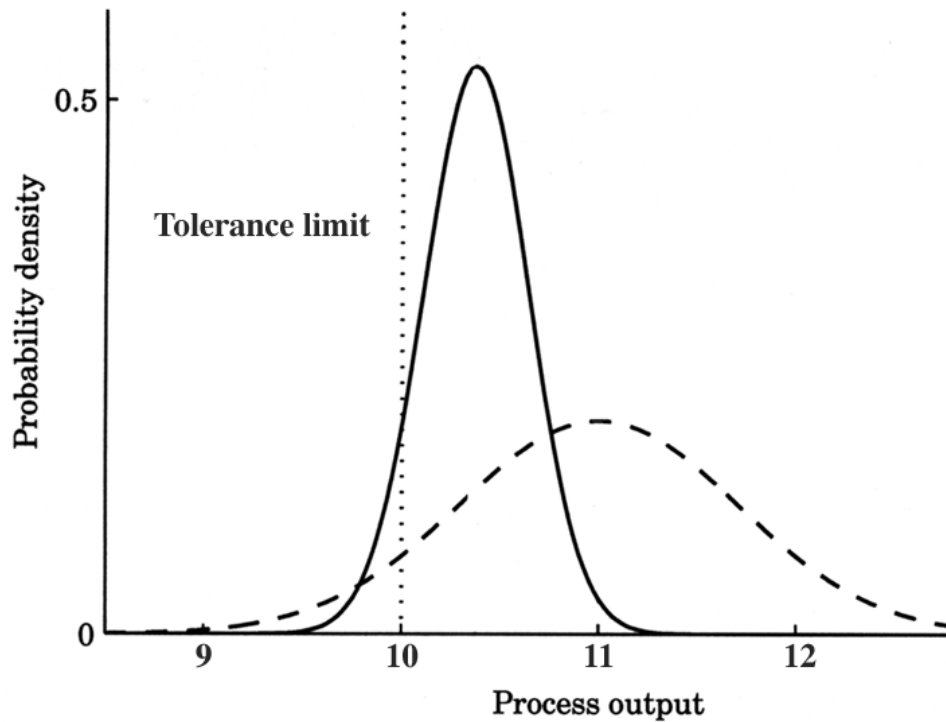
> "Process operations and control have a tremendous impact on the profitability of a manufacturing operation. In some cases, they can determine the economic viability of a manufacturing facility. For example, Du Pont's Process Control Technology Panel has estimated that if Du Pont were to extend the degree of computer process control that has been achieved at a few of its plants across the entire corporation, it would save as much as half a billion dollars a year in manufacturing costs. If Du Pont's numbers are representative, the entire chemical industry could save billions of dollars each year through more widespread application of the best available process control. This could be the single most effective step that the U.S. Chemical process industry could take to improve its global competitive position in manufacturing."

According to the study, research opportunities in process operations and control lie in three areas;

- collection of information through process measurements;

- interpretation and communication of information by use of process models;

- utilization of information through control algorithms and control strategies for both normal and abnormal operation.

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[1]Frontiers in Chemical Engineering: Research needs and opportunities, National Academy Press, Washington 1988.

Figur 1 Illustrates the benefits by improved steady state regulation.

Among the factors that give the benefits are: improved quality, increased production rate, lower consumption of energy and raw material, faster production changes and improved safety. There has not been a strong interest in manufacturing in the pharmaceutical industry, where the focus has been on development of new drugs. However, the industry is now facing many challenges: global competition, vertical integration, demands on more flexible production, reduced consumption of raw material, reduced emissions, and increased demands on quality. Effective use of information technology is one way to meet these challenges.

2. Regulation

Regulation of quality variables in continuous production is one of the most common uses of process control. The idea is very simple, measure the important quality variables and adjust the process continuously so that the variations are reduced.

Where are the benefits?

The benefits obtained can be illustrated in Figure 1. The figure shows the probability distribution of a quality variable for two controllers. One controller gives a lower variance than the other. In practically all manufacturing situations there is a lower limit to a quality variable and a specification that says that only a small percentage of the production can be below that limit. This is illustrated by the test limit 10 in the Figure. Apart from the direct benefits in having smaller variations there is also another effect. With the controller having smaller variance it is possible to operate closer to the test limits. The setpoint in the Figure can be reduced from 11 to 10.4. This means that less raw material is used. For a

process in continous operation even small reductions may give considerable pay off.

How is it done?

To perform good steady state regulation it is necessary to have sensors that measure the quality variables on-line and actuators that can influence the quality. The control system typcially consists of sensors, actuators, a computer and devices for connectiong these components. The core of the system is a control algorithm in the computer that computes appropriate values of the manipulated variables based on the information from the sensors. There are two standard approaches to obtain suitable control algorithms. One possibility is to use a standard control algorithm, for example a PID controller and to adjust its parameters empirically. The other method is based on mathematical models describing the statistical nature of the quality variations, and the dynamic relations between measured variable and actuators are also required. If these relations are known it is possible both to tell how much the fluctuations can be reduced and what the optimal control algorithm should look like.

In automatic control there are well developed techniques to acquire that knowledge directly from experiments, see Åström and Wittenmark (1997). Two different experiments are typically performed. In one experiment we simply record the fluctuations obtained during normal operation. In the other experiment the acutators are perturbed in an irregular manner and the variations in quality variables are observed. By analysing that experiment it is possible to determine mathematical models that tell the relations between quality and the manipulated variables. By analysing the data from both experiments it is possible both to estimate the improvements that can be achieved in steady state regulation and a control algorithm that achieves the results.

Obstacles

Major factors that limit the achievable performance are: availability of sensors and actuators and the dynamic characteristics of the relation between manipulated variables and true process quality.

It is often very difficult to measure true process quality on-line. Analytic sensors may not be available, they may require sampling, which means that the measurement only reflects the quality of a small fraction of the product. There may also be substantial delays before the measurement is obtained. For these reasons it is common practice to use a range of sensors, some may give fast indications of changes with poor absolute precision, other may give very accurate absolute values with long time delays. There are useful methodologies to combine the outputs of different sensors with mathematical models. For the pharmaceutical industry it is particularly interesting that the development of process analytical chemistry has given new spectroscopic sensors. Combined with powerful statistical techniques, Wold (1978) and MacGregor (1997), this permits on-line measurement of composition and structure.

Traditional manufacturing processes often lack appropriate actuators that permit intentional manipulation of quality variables. There are however many interesting possibilities in design of new processing equipment, one possibility is to arrange the production process to allow mixing of product streams with different properties.

It may be difficult to obtain good regulation even when sensors and actuators are available because the relations between sensors and actuators may cause

difficulties. Long time delays between sensing and acutation and large mixing vessels are typical obstacles. When introducing control systems it is therefore often advisable to make modifications of the process equipment.

Tuning and adaptation

The techniques for dynamic modeling and analysis of fluctuations in quality variables can be combined to give systems with higher automation levels where the controller is automatically adjusted to changing process conditions. These techniques are particularly well suited to continous regulation of quality variables, see Åström (1996). The methods can also be used to adjust standard controllers.

3. Batch Control

Most processes in the pharmaceutical industry are performed as a sequence of batch processes. A major development step is the scale up from the laboratory to full scale production via a pilot plant process. Automation and information technology are of increasing importance at all three stages, and a lot of effort goes into the scale up of instrumentation and standard operating procedures.

The production of pharmaceuticals is subject to strict governmental regulations. The organic fine chemicals often require processes that are potentially hazardous. Some reactions are exothermal and sufficient margins in cooling must be available. Regular HAZOP analyses should include the interplay between the process and the automatization system, see Srinivasan and Venkatasubramanian (1996). Some processes contain steps where genetically modified microorganisms are used. In this field there is a long tradition of safety regulations to prevent the release to the environment of modified genetic material.

A standard for current Good Manufacturing Practices is set by the U.S. Food and Drug Administration. Such rules require validation of the production process and equipment as well as the Standard Operating Procedures. Similar requirements are set in quality assurance certification and ISO 9001.

Information technology and automation is utilized for the formalization of the production and inspection protocols. Such manufacturing execution systems are nowadays often developed using the ISA S88 standard for recipe-driven batch control, e.g. Dorresteijn *et al.* (1997). Many drug companies are active players in the continued work in the standardization committees together with the manufacturer of automatization systems and university research departments.

A sequence of control tasks

It is important to have a high reproducibility in the different production steps. Automatic control can be used to maintain identical enviromental conditions during each step. Biotechnology processes are often run in fed-batch, and a feed controller may have to match an exponentially growing feed demand. In Sonnleitner (1997) it is discussed how to design bioprocesses to achieve a high degree of reproducibility. High quality equipment should be used together with automated operating procedures including a minimum of operator interaction. New measurement devices give new possibilities for control, but also new challenges in controller design and tuning.

An exemple

In the production of bakers' yeast growing on molasses it is possible to adjust the feeding profile to variations in the starter culture in order to reduce the variation

in the environmental conditions. This was done using feedback from a sensor for the by-product ethanol in Hagander *et al.* (1990). A well-tuned PID-controller gave good control, and it was valuable to base the choice of controller parameters on a crude dynamical model for the process. This procedure has also been used for full scale production of growth-factors using genetically modified yeast. The controller parameters were chosen using scaling based on the parameter values in a model of the production process. In this way there was an improvement in both reproducibility and in product yield.

Statistical Process-Control

Large amounts of product quality data is accumulated in order to monitor the process operating performance, and recently multivariate statistical methods are used to combine such data with standard process variable data. This is often called Statistical Process-Control, MacGregor and Kourti (1995). Quality and safety assessment requires reliable measurement techniques, preferably automated for consistency. An example is in protein production, where you monitor the production yield and purity, e.g. Chandwani *et al.* (1997). It is then tempting to try to modify the way you run the process, when you experience changes.

4. Diagnostics and Assessment

Supervision of production is a key factor in high quality production. Systems for fault dectection and isolation are traditionally not part of a control system. Alarms are typically based on monitoring of deviations of specific variables. Often there is only one alarm level, but several different levels may be used in sophisticated systems. Alarm overload is a real concern in large systems. One fault may give rise to a very large number of alarms, and it may be hard to determine the root of the difficulty because of the abundance of alarms.

It is a substantial advantage to integrate diagnostics and control. The signals in the control loop give very useful information of the whole range of systems that are connected in the feedback loop, the sensors, the actuators, the process, the computer and the interfaces. Very efficient diagnostics can be obtained by analysing the signals in the control loop, see Åström (1991) and Hägglund (1995).

Computer controlled systems in the process industry acquire large amounts of data. A large factory may have samples of thousands of signals every second! In spite of this very large amount of data it is very difficult to extract useful information from the system. A typical situation occurs when automation systems have to be replaced. With present systems it is very hard to get the critical information about the old system, so that the new system can run at least as well as the old system, when it is starting. Very much can be improved in this respect if new systems are designed carefully. It is for example possible to install algorithms for loop assessment, which continuously analyse individual control loops to determine there key characteristics. These can be compared with previous data for diagnostics relating to processes and raw material. Similarly it is possible to devise performance assessment schemes that continuously monitor the performance of control loops and makes comparisons with estimates of best possible regulation performance. This is discussed in Passino and Antsaklis (1992) and Åström and Årzén (1993). Indices that indicate deviation from ideal performance are developed in Desborough and Harris (1992).

5. Conclusions

Process control is an enabling technology to achieve high qualitative unit operations. The paradigms and tools of process control are valuable also on the level of production supervision. For rejected batches analysis should be done to find the cause of the failures, and it natural to see the resulting changes in the Standard Operating Procedure as control actions. The main challenge in the safety critical process industry is to implement methods for quality improvement by process changes still maintaining a high degree of safety.

The dynamic development of process analytical chemistry and spectroscopic techniques has the potential to provide a new generation of sensors that can be used on-line in production. Combined with the advances in process control there seems to be a good potential for dramatic progress in production methods for the pharmaceutical industry.

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